The Correlation between Antibiotic Consumption and Multidrug-Resistant Organism Infection in Tuanku Ampuan Najihah Hospital (HTAN)

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Abstract

Introduction: Antibiotic resistance is a global health issue. The increasing trend of multidrug-resistant organism (MDRO) infections has become a main concern because it will lead to increased healthcare cost, failure of antibiotic treatment and increased mortality rate.

Objectives: To assess the correlation between antibiotic consumption and multidrug-resistant (MDR) infections (extended spectrum beta-lactamase (ESBL)-producing bacterial and MDR *Acinetobacter*) in Tuanku Ampuan Najihah Hospital from 2014 to 2016.

Method: A retrospective study was conducted. Antibiotic consumption data was expressed as the defined daily dose (DDD)/1000 inpatient-day in 6 months while MDRO infection was expressed as the number of ESBL-producing bacterial and MDR *Acinetobacter* cases in 6 months. The correlation between antibiotic consumption and MDRO infection was evaluated using Pearson's correlation coefficient or Spearman rank-order correlation.

Results: The total antibiotic consumption decreased by 60.09% from 458.98 DDD/1000 inpatient-days in Jan-June 2014 to 178.59 DDD/1000 inpatient-days in July-December 2016. The greatest reduction in consumption was observed in carbapenems (-87.91%). During the same period, ESBL-producing bacterial infections increased by almost three-fold but the increase in MDR *Acinetobacter* infections was minimal. The increment of ESBL infection was seen in the Medical, Surgical and Orthopaedic wards while most of the MDR *Acinetobacter* infections were from the Intensive Care Unit / Coronary Care Unit (ICU/CCU) (76%). Statistically significant strong negative correlations were found between ESBL infections and consumption of ciprofloxacin (r=-0.930, p=0.007) and moxifloxacin (r=-0.873, p=0.023). There was a significant strong positive correlation between piperacllin/tazobactam consumption and MDR *Acinetobacter* infections (r=0.839, p=0.037) in ICU/CCU.

Conclusion: Our study did not observe uniform trends in the correlation between the antibiotic consumption and MDRO infections. Besides the strict control of antibiotics use, other factors may also be important in suppressing the emergence of MDRO. More studies should be carries out to help planning for strategies in combating antibiotic resistance.

Keywords: antibiotic consumption, correlation, ESBL, MDR *Acinetobacter*

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Introduction

Antibiotic resistance is an alarming global issue threatening our health (1). Overuse and misuse of antibiotic have been identified as the main cause of the development and spread of antibiotic resistance (2). The call for actions to combat antibiotic resistance is a matter of urgency because of the drying up of the antibiotic pipelines, and the current antibiotics are losing their effectiveness rapidly as a result of the antibiotic resistance (3).

The common multidrug-resistant organisms (MDRO) are methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and certain Gram-negative bacilli (GNB) such as extended spectrum beta-lactamases (ESBL)-producing organisms and multidrug-resistant (MDR) *Acinetobacter* (4). In the recent years, infections due to Gram-negative bacteria, especially MDRO, have increased continuously (5). The increasing trend of MDR infections has become a main concern because it leads to the increased risk in

transplant and other surgical procedures that are dependent on the effectiveness of antibiotic, failure of antibiotic treatment, increased healthcare cost due to costlier new antibiotics or prolonged hospitalisation, and increased mortality rate (2,6).

ESBLs are enzymes produced by some Gram-negative bacteria such as *Escherichia coli* and *Klebsiella* species. These enzymes have the ability to hydrolyse extended spectrum cephalosporins such as ceftazidime, ceftriaxone and cefotaxime which commonly act as first line antibiotics for many infections in the hospital. Therefore, any delay in the identification and failure to treat severe infection caused by ESBL-producing bacteria would lead to increased morbidity and mortality (7). Recently, *Proteus mirabilis* also emerged as one of the producers of ESBL (8). Hawser *et al*. found that countries in Asia-Pacific region showed the highest level of antimicrobial resistance. As high as 42.2% of *E. coli* and 35.8% of *Klebsiella* species among the Gram-negative bacilli collected from intra-abdominal infections in the Asia-Pacific region were found to be ESBL positive (9). In Malaysia, the estimated prevalence of ESBLs was 7% to 19% for *E. coli* and 27% to 38% for *Klebsiella* species (10,11).

MDR *Acinetobacter* refers to any *Acinetobacter* species that is resistant to at least one agent in at least three different classes of antimicrobial agents (12). *Acinetobacter* has the ability to survive on both dry and moist inanimate surfaces for as long as five months. It can also grow at different ranges of temperatures and pH values (13). Therefore, its ability to survive in the hospital environment and persist for a long period enable it to be the frequent cause of healthcare associated infection such as pneumonia, meningitis and urinary tract infection (14).

Previous antibiotic exposure may exert selective pressure to eliminate all sensitive strains, which may in turn lead to the development of antibiotic resistance (7,15). For example, excessive cephalosporins use may lead to the emergence of ESBL-producing organisms (7). The most used antibiotic groups in the hospitals is known to be third generation cephalosporins, which were reported to exert predominant selective pressure for the development of resistant *E. coli* and *Klebsiella pneumoniae*. Several studies had also shown positive correlations between quinolones and third-generation cephalosporins use and the acquisition of ESBL-producing strain (7,16,17). Similarly, prior exposure of broad-spectrum antimicrobial agents, such as second and third generation cephalosporins, carbapenems, and fluoroquinolones, is one of the major risk factors for the acquisition of the MDR strains of *Acinetobacter* (5,13,18,19).

To our knowledge, limited studies have been conducted in Malaysia to assess the correlation between antibiotic consumption and MDRO infections. This study aimed to determine the antibiotic consumptions, number of MDR infections, and to assess the correlation between antibiotic consumptions and MDRO infections in the past three years (2014-2016) in Tuanku Ampuan Najjihah Hospital (HTAN). The findings from this study are important to give an overview on the related topic, and to identify possible strategies for future planning in reducing the emergence of MDRO infections.

Method

A retrospective study was conducted from February to December 2017 in HTAN, Kuala Pilah, Negeri Sembilan, a tertiary care major specialist hospital with 317 beds. Three-year data from year 2014 to 2016 was collected for the purpose of this study. Antibiotic consumption and MDRO infection data from all wards, except the emergency department, paediatric and neonatal wards, were included in this study.

Antibiotic Consumption

Antibiotic consumption data was obtained from the Pharmacy Department. These data were extracted from the data collected by the Pharmacy Department for the National Surveillance of Antibiotic Usage reports. These figures comprised actual consumption data rather than purchasing data. Intravenous antibiotics that were frequently associated with the emergence of antibiotic resistance group and available in HTAN were included in this study, namely carbapenems (imipenem and meropenem), quinolones (ciprofloxacin and moxifloxacin), cephalosporins (cefuroxime, ceftazidime, cefoperazone, ceftriaxone, cefotaxime, and cefepime) and beta-lactam/beta-lactamase inhibitor (cefoperazone/sulbactam, ampicillin/sulbactam, piperacillin/tazobactam and amoxicillin/clavulanic acid). The antibiotic consumption data was expressed as defined daily dose (DDD) per 1000 inpatient-days consumed in every 6 months, calculated based on the World Health Organisation ATC/DDD Index (20).

MDRO Infections

The MDRO tracked were ESBL-producing bacteria (ESBL *E. coli,* ESBL *Klebsiella,* ESBL *Proteus*) and MDR *Acinetobacter*. Data was expressed as the number of cases of ESBL-producing bacteria and MDR *Acinetobacter* infections in every 6 months. ESBL-producing bacterial infection data were extracted from the hospital Laboratory Information System (LIS). ESBL infections were defined from ESBL isolates grew from sterile cultures (blood culture, tissue culture, bone culture, cerebrospinal fluid culture). Non-sterile isolates like sputum culture, tracheal aspirate culture, urine culture, pus culture and swab culture were not considered due to the high chance of being a colonizer or contaminant. On the other hand, MDR *Acinetobacter* infections was defined as all MDR *Acinetobacter* infections treated in the ward as the majority of the laboratory cultures were from non-sterile cultures and tend to be repetitive. Therefore, MDR *Acinetobacter* infections data were extracted from the treated MDR *Acinetobacter* cases captured by the Clinical Pharmacy Unit for monitoring purpose since year 2014.

Statistical Analysis

Pearson's correlation or Spearman rank-order correlation coefficient was conducted to assess the correlation between antibiotic consumptions and respective MDRO infections. It is considered statistically significant when the p value is less than 0.05, with a confidence interval of 95%. A correlation coefficient (r) of less than 0.3 indicates a weak correlation, 0.3 to 0.7 indicates moderate correlation and more than 0.7 indicates a strong correlation.

Results

Antibiotic Consumption

Antibiotic consumptions in HTAN from 2014 to 2016 were presented in Table 1. The total antibiotic consumption decreased tremendously from 458.98 DDD per 1000 inpatient-days in Jan-June 2014 to 178.59 DDD per 1000 inpatient-days in July-December 2016 (-61.09%). From 2014 to 2016, cephalosporin group was the main antibiotic group consumed followed by beta-lactam/beta-lactamase inhibitor group. Overall, all antibiotic consumptions had decreased from 2014 to 2016. The greatest reduction in consumption was observed in the carbapenem group (-87.91%), followed by quinolone group (-69.08%), cephalosporin group (-60.73%) and beta-lactam/beta-lactamase inhibitor group (-55.57%). In terms of the individual antibiotic, the greatest reduction in consumption was observed in moxifloxacin (-100%), imipenem (-100%), ceftriaxone (-85.48%), meropenem (-83.28%) and piperacillin/tazobactam (-73.22%).

MDRO Infections

The number of ESBL *E. coli*, ESBL *Klebsiella*, ESBL *Proteus* and MDR *Acinetobacter* infections were summarised in Table 2. Among the four types of infections, MDR *Acinetobacter* showed the highest cases of infection (38.10%) followed by ESBL *Klebsiella* (36.11%).

Table 3 showed the trend of total ESBL and MDR *Acinetobacter* infections in HTAN according to clinical disciplines from 2014 to 2016. From January-June 2014 to July-December 2016, almost three-fold increment was observed for ESBL infections but the increase in MDR *Acinetobacter* infections was minimal. The increment in ESBL infections was notable in the medical, surgical and orthopaedic disciplines.

Table 1: Antibiotic consumption (DDD / 1000 inpatient-day) in HTAN from 2014 to 2016

Antimicrobial Agents	Antibiotic Consumption (DDD / 1000 patient-day)						Difference (%) [c]
	2014 Jan-Jun [a]	2014 Jul-Dec	2015 Jan-Jun	2015 Jul-Dec	2016 Jan-Jun	2016 Jul-Dec [b]	
Quinolone							
Ciprofloxacin	13.64	9.39	6.31	3.02	4.76	4.39	-67.82
Moxifloxacin	0.56	0.60	0.15	0.00	0.11	0.00	-100
Total	14.2	9.99	6.46	3.02	4.87	4.39	-69.08
Cephalosporin							
Ceftazidime	34.74	34.52	20.45	37.32	25.03	19.80	-43.01
Cefepime	21.87	27.07	10.46	10.38	14.47	8.24	-62.32
Ceftriaxone	84.94	101.43	90.67	68.34	35.13	12.33	-85.48
Cefotaxime	1.52	0.59	0.21	0.32	0.11	0.51	-66.45
Cefuroxime	85.63	72.03	42.8	29.31	46.82	49.23	-42.51
Cefoperazone	6.03	9.44	7.54	5.91	5.55	2.08	-65.51
Total	234.73	245.08	172.13	151.58	127.11	92.19	-60.73
Beta-lactam/beta-lactamase Inhibitor							
Cefoperazone/sulbactam	5.05	3.53	0.52	3.63	1.96	1.82	-63.96
Ampicillin/sulbactam	90.61	90.79	81.59	25.95	82.84	42.36	-53.25
Piperacillin/tazobactam	23.82	25.85	29.45	14.10	20.87	6.38	-73.22
Amoxicillin/clavulanic acid	55.58	45.50	54.27	19.24	47.39	27.22	-51.03
Total	175.06	165.67	165.83	62.92	153.06	77.78	-55.57
Carbapenem							
Imipenem	9.69	5.18	5.56	3.11	2.83	0.00	-100
Meropenem	25.30	36.38	22.58	13.03	15.64	4.23	-83.28
Total	34.99	41.56	28.14	16.14	18.47	4.23	-87.91
Total Antibiotic Consumption	458.98	462.30	372.56	233.66	303.51	178.59	-61.09

Note: c = (b-a) / a x 100

Table 2: Number of ESBL *E. coli*, ESBL *Klebsiella*, ESBL *Proteus* and MDR *Acinetobacter* infections (n=252)

Infection	Number of Infection, n						Total, n (%)
	2014 Jan-Jun	2014 Jul-Dec	2015 Jan-Jun	2015 Jul-Dec	2016 Jan-Jun	2016 Jul-Dec	
ESBL	10	20	25	30	34	37	156 (61.90)
ESBL *E. coli*	0	4	7	8	11	18	48 (19.04)
ESBL Klebsiella	10	16	15	18	18	14	91 (36.11)
ESBL *Proteus*	0	0	3	4	5	5	17 (6.75)
MDR Acinetobacter	15	18	16	9	19	19	96 (38.10)
Total	25	38	41	39	53	56	252

Table 3: Number of ESBL and MDR *Acinetobacter* infections in HTAN according to disciplines from 2014 to 2016 (n=252)

Discipline	Number of Infection, n						Total, n (%)
	2014 Jan-Jun	2014 Jul-Dec	2015 Jan-Jun	2015 Jul-Dec	2016 Jan-Jun	2016 Jul-Dec	
ESBL							
Medical	3	5	9	10	7	10	44 (28.2)
Surgical	2	3	4	5	13	10	37 (23.7)
Orthopaedics	1	8	6	7	4	11	37 (23.7)
ICU/CCU	4	4	5	4	9	5	31 (19.9)
O&G	0	0	1	4	1	1	7 (4.5)
Total	10	20	25	30	34	37	156 (61.9)
MDR *Acinetobacter*							
Medical	3	3	2	0	4	2	14 (14.6)
Surgical	0	1	0	0	2	2	5 (5.2)
Orthopaedics	1	1	0	0	0	1	3 (3.1)
ICU/CCU	11	13	14	9	12	14	73 (76.0)
O&G	0	0	0	0	1	0	1 (1.1)
Total	15	18	16	9	19	19	96 (38.1)
Total MDRO Infection	25	38	41	39	53	56	252

Abbreviation: ICU/CCU – Intensive Care Unit/Coronary Care Unit; O&G – Obstetrics and Gynaecology; MDRO – multidrug-resistant organism

Correlation between Antibiotic Consumption and MDR Infection

The correlations between antibiotic consumption and MDRO infection were summarised in Table 4. There were negative correlations between all the antibiotics and ESBL infections. Strong negative correlations were observed between ESBL infections with ciprofloxacin, moxifloxacin, cefepime, ceftriaxone, cefotaxime and cefuroxime, but statistically significant correlation was only observed in ciprofloxacin and moxifloxacin. On the other hand, there were moderate positive correlations between MDR *Acinetobacter* infections with ampicillin/sulbactam and amoxicillin/clavulanic acid, but all were not statistically significant. Moderate negative correlation was observed between ceftazidime consumptions and MDR *Acinetobacter* infections, and it was not statistically significant as well.

In view of majority of the MDR *Acinetobacter* infections were from the ICU/CCU, a sub-analysis of correlation test was done between MDR *Acinetobacter* infections and antibiotic consumptions in ICU/CCU (Table 5). The findings showed statistically significant positive strong correlation between MDR *Acinetobacter* infections with piperacillin/tazobactam consumption in ICU/CCU. Positive moderate but not statistically significant correlations were observed between MDR *Acinetobacter* infections with cefuroxime, ampicillin/sulbactam and amoxicillin/clavulanic acid consumptions.

Table 4: Correlation between antibiotic consumption and MDRO infections in HTAN

Antibiotic	ESBL		MDR *Acinetobacter*	
	r	P-value	r	P-value
Quinolone				
Ciprofloxacin	-0.930	0.007 *	0.153	0.772
Moxifloxacin	-0.873	0.023 *	0.187	0.722
Cephalosporin				
Ceftazidime	-0.556	0.252	-0.623	0.186
Cefepime	-0.739	0.093	0.195	0.711
Ceftriaxone	-0.791	0.061	-0.330	0.523
Cefotaxime	-0.799	0.056	-0.074	0.889
Cefuroxime	-0.791	0.061	0.361	0.482
Cefoperazone	-0.575	0.232	-0.122	0.818
Beta-lactam/beta-lactamase Inhibitor				
Cefoperazone/sulbactam	-0.649	0.163	-0.392	0.442
Ampicillin/sulbactam	N.A.	N.A.	0.541	0.268
Piperacillin/tazobactam	N.A.	N.A.	0.068	0.898
Amoxicillin/clavulanic acid	N.A.	N.A.	0.440	0.382
Carbapenem				
Imipenem	N.A.	N.A.	-0.203	0.699
Meropenem	N.A.	N.A.	0.075	0.887

* Significant correlation between antibiotic consumption and MDR infections

Table 5: Correlation between antibiotic consumption and MDRO infection in ICU/CCU discipline in HTAN

Antibiotic	MDR *Acinetobacter*	
	r	P-value
Quinolone		
Ciprofloxacin	0.129	0.808
Moxifloxacin	0.092	0.862
Cephalosporin		
Ceftazidime	0.222	0.672
Cefepime	-0.263	0.615
Ceftriaxone	-0.106	0.842
Cefotaxime	-0.580	0.228
Cefuroxime	0.492	0.321
Cefoperazone	-0.582	0.226
Beta-lactam/beta-lactamase Inhibitor		
Cefoperazone/sulbactam	-0.795	0.059
Ampicillin/sulbactam	0.560	0.248
Piperacillin/tazobactam	0.839	0.037 *
Amoxicillin/clavulanic acid	0.512	0.299
Carbapenem		
Imipenem	-0.111	0.835
Meropenem	0.112	0.833

* Significant correlation between antibiotic consumption and MDR *Acinetobacter* infection

Discussion

The consumption of antibiotics in HTAN was found to decrease tremendously over the past three years of 2014 to 2016, especially in the carbapenem group. Total ESBL-producing bacterial infections increased gradually at the same period of time but not much changes was observed in terms of MDR *Acinetobacter* infections. Negative correlations were found between ESBL infections and quinolones use while positive correlations were found between MDR *Acinetobacter* infections and piperacillin/tazobactam consumption in the ICU/CCU.

The overall decreasing consumption of these antibiotics was due to the implementation of Antimicrobial Stewardship (AMS) in HTAN since January 2015. The programme aimed to improve patient outcomes and optimise antibiotic therapy with the hope to limit the emergence of antibiotic resistance, and hence to reduce MDRO infections without adversely impacting the quality of patient care (17). AMS activities conducted included antibiotic rounds by the medical consultants and clinical pharmacists weekly to fortnightly, restrictions in antibiotic use such as carbapenem use restriction, encouragement of intravenous to oral antibiotic conversion and de-escalation of antibiotics based on patient's condition and culture and sensitivity test results. Furthermore, antibiotic request form was required for all newly started broad-spectrum antibiotics and justification for their continuation after 72 hours of initiation. The antibiotics involved were imipenem, meropenem. piperacillin/tazobactam, cefoperazone/sulbactam, cefepime, cefoperazone, ceftazidime and ceftriaxone.

Previous studies suggested that prior exposure to third generation cephalosporins and quinolones could lead to the emergence of ESBL-producing strains, and thus the restriction of antibiotics use is needed to reduce the level of antibiotic resistance (7,16,17). Our result of decreasing antibiotic consumption with increasing ESBL infection was similar to the study conducted by Hyle *et al*. (22), which showed that prior antibiotic use was not independently associated with ESBL *E. coli* and *Klebsiella* infections. The only independent risk factor for ESBL *E. coli* and *Klebsiella* was the species of infecting organism. Molecular analysis from their study also indicated close genetic relatedness of *K. pneumoniae* isolates and this suggested that horizontal spread is important in the emergence of ESBL *E. coli* and *Klebsiella*. The antibiotic-resistance genes will still exist in the environment through the bacteria that have since replicated even if the specific antibiotic is no longer introduced (23). This may explain why ESBL infection in HTAN was still high despite the reduction in all antibiotic consumption.

Results from our study also suggested that there might be other causes besides antibiotic consumption that led to the increase in ESBL infections in HTAN. Previous studies have shown that the risk factors for nosocomial acquisition of ESBL-producing organism infections were age 65 years or higher, dementia, diabetes, accommodation in a ward or room with other patients with ESBL-producing organisms infection, history of recent hospitalisation, prolonged hospital stay and prolonged duration of presence of medical devices in the patient body such as urinary catheters, endotracheal tubes and central venous lines (19,24,25). In order to reduce the risk of transferring MDRO from colonisation to infection sites, the frequency of procedures that carry such risk should be minimised (26).

Administration of broad-spectrum antimicrobial agents, particularly third-generation cephalosporins, carbapenems, and fluoroquinolones were usually considered as one of the major risk factors for the acquisition of the MDR strains of *Acinetobacter* (5,13,19). Carbapenem consumption could modify the bacteria flora in patients and encouraged the infection and/or colonization of resistant bacteria (19). Nevertheless, our results only showed significant positive correlation between consumption of piperacillin/tazobactam and MDR *Acinetobacter* infections. This was similar with the study done by Chan *et al*. (27) which showed that prior use of piperacillin/ tazobactam was also found to be a significant risk factor for the emergence of extensively drug-resistant *Acinetobacter baumannii*.

The increasing incidence of MDR *Acinetobacter* infections in hospitals might be due to the ability of this organism to survive in dry inanimate surfaces for a long period, from three days to five months. They possess fimbriae or lipopolysaccharide side chains that can attach to the human epithelial cells and form biofilm when they are in contact with plastic and glass surfaces (28,29). These mechanisms facilitate the colonisation of *Acinetobacter* in patients or equipments used in medical care such as catheter. Therefore, ICU patients can acquire MDR *Acinetobacter baumannii* from an ICU room previously occupied by a carrier of these bacteria (30). Other risk factors included prolonged hospital stays, support with mechanical ventilation and exposure to infected or colonised patient in neighbouring hospital (13).

To minimize the horizontal spread of MDRO, greater attention should be placed on the early identification of such isolates and reducing the transmission through active infection-control surveillance in the hospital. The modes of transmission of MDRO among the patients include airborne, direct or indirect contact with contaminated equipment, contaminated environment or the contaminated hands of healthcare workers in the hospital. Failure of health care workers to practice aseptic technique (e.g., hand washing and changing gloves after examining a patient) was a leading contributor to the spread of drug-resistant organisms in hospitals (31). An adequate infection-control level of the nursing staffs and correct hand hygiene practices are important in minimising the risk of inter-patient spread of infections. Screening should be done for patient transferred from

other hospitals or residential homes and to detect readmitted patient who are previously found to be a carrier of MDRO (26). This is important because HTAN was part of the hospital cluster programme in Malaysia since 2016. Within a hospital cluster, resources of a few hospitals could be shared and patients may be transferred between the hospitals to improve the clinical outcome and efficiency of resources use.

This was a preliminary study done retrospectively in a non-electronic based hospital. The antibiotic consumption data was recorded manually, thus the chance of discrepancy may exist. Secondly, the acquisition of antibiotic resistance and the emergence of ESBL-producing bacteria and MDR *Acinetobacter* may not occur parallelly with the antibiotic consumption. Furthermore, the reduction of ESBL and MDR *Acinetobacter* infections may take some time to be reflected from the reduced antibiotic consumption. Hence, the results should be interpreted with caution.

Conclusion

The consumption of antibiotics in HTAN has reduced from 2014 to 2016. The number of ESBL-producing bacterial infections has increased during the same period but the changes in the number of MDR *Acinetobacter* infections was minimal. The cases of ESBL infections were negatively correlated with quinolones use while MDR *Acinetobacter* infections were positively correlated with piperacillin/tazobactam consumption in the ICU/CCU. This showed that besides the strict control and reducing the consumption of antibiotics, other factors may also be important in suppressing emergence of MDR organisms. More studies should be carries out to identify the other possible contributing factors in order to aid future planning of strategies in combating antibiotic resistance.

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Conflict of Interest Statement

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References

1. World Health Organization. The evolving threat of antimicrobial resistance: Options for action. WHO Publ [Internet]. 2012;1–119. Available from: http://www.ijmr.org.in/article.asp?issn=0971-5916;year=2014;volume=139;issue=1;spage=182;epage=183;aulast=Kapi
2. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum b -lactamase production in Enterobacteriaceae bacteraemia : a systematic review and meta-analysis. 2007;(September):913–20.
3. Davies J, Davies D. Origins and Evolution of Antibiotic Resistance. Microbiol Mol Biol Rev [Internet]. 2010;74(3):417–33. Available from: http://mmbr.asm.org/cgi/doi/10.1128/MMBR.00016-10
4. Siegel JD, Rhinehart E, Jackson M, Chiarello L. Management of multidrug-resistant organisms in health care settings , 2006. 2007;
5. Lai CC , Wang CY, Chu CC, Tan CKi, Lu CL LY, Huang YT LP and HP. Correlation between antibiotic consumption and resistance of Gram-negative bacteria causing healthcare-associated infections at a university hospital in Taiwan from 2000 to 2009. 2011;(March):1374–82.
6. Sun L, Klein EY, Laxminarayan R. Seasonality and Temporal Correlation between Community Antibiotic Use and Resistance in the United States. 2012;55:687–94.
7. Du B, Long Y, Liu H, Chen D, Liu D, Xu Y, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bloodstream infection : risk factors and clinical outcome. 2002;1718–23.
8. Pagani L, Migliavacca R, Pallecchi L, Matti C, Giacobone E, Amicosante G, et al. Emerging Extended-Spectrum ℕ -Lactamases in Proteus mirabilis. 2002;40(4):1549–52.
9. Program S, Hawser SP, Bouchillon SK, Hoban DJ, Badal RE, Hsueh P, et al. Emergence of High Levels of Extended-Spectrum- ℕ -Lactamase-Producing Gram-Negative Bacilli in the Asia-Pacific Region : Data from the Study for Monitoring Antimicrobial Resistance Trends. 2009;53(8):3280–4.

10. Othman S, Ramli R, Canselor H, Mukhriz T. Detection of CTX-M-type ESBLs Escherichia coli at Universiti Kebangsaan Malaysia Medical Centre. 2016;(August).
11. Sharma M, Pathak S, Srivastava P. Prevalence and antibiogram of Extended Spectrum beta-Lactamase (ESBL) producing Gram negative bacilli and further molecular Characterization of ESBL-producing Escherichia coli and Klebsiella spp . 2013;2173–7.
12. Magiorakos A, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect [Internet]. 2011;18(3):268–81. Available from: http://dx.doi.org/10.1111/j.1469-0691.2011.03570.x
13. Karageorgopoulos DE, Falagas ME. Current control and treatment of multidrug-resistant Acinetobacter baumannii infections. Lancet Infect Dis [Internet]. 8(12):751–62. Available from: http://dx.doi.org/10.1016/S1473-3099(08)70279-2
14. Manchanda V, Sanchaita S. Multidrug Resistant Acinetobacter. 2010;(3).
15. Urba´nek, K.M., Kola´r, M, Loveckova´ Y., Strojil J, Antava´ L. Influence of third-generation cephalosporin utilization on the occurrence of ESBL-positive Klebsiella pneumoniae strains. 2007;403–8.
16. Saurina G, Quale JM, Manikal VM, Oydna E, Landman D. Antimicrobial resistance in Enterobacteriaceae in Brooklyn , NY : epidemiology and relation to antibiotic usage patterns. 2000;895–8.
17. Paterson DL, Bonomo RA. Extended-Spectrum ␣ -Lactamases : a Clinical Update. 2005;18(4):657–86.
18. Janahiraman S, Aziz MN FK, Hon SP, Yang LB R V, Shamsuddin AF. Resistance patterns of multidrug resistant Acinetobacter baumannii in an ICU of a tertiary care hospital , Malaysia. 2015;31(6):1383–8.
19. Xu J, Sun Z, Li Y, Zhou Q. Surveillance and Correlation of Antibiotic Consumption and Resistance of Acinetobacter baumannii complex in a Tertiary Care Hospital in Northeast China , 2003 – 2011. 2013;1462–73.
20. World Health Organization (WHO). ATC/DDD index. WHO Collaborating Centre for Drug Statistics Methodology.
21. Pharmaceutical Services Division. Protocol on Antimicrobial Stewardship Program in Healthcare Facilities. 2014;1–57.
22. Hyle EP, Lipworth AD, Zaoutis TE, Nachamkin I, Fishman NO, Bilker WB, et al. Risk Factors for Increasing Multidrug Resistance among Extended-Spectrum b -Lactamase – Producing Escherichia coli and Klebsiella Species. 2005;6021:1317–24.
23. Martinez JL. Environmental pollution by antibiotics and by antibiotic resistance determinants. Environ Pollut [Internet]. 2009;157(11):2893–902. Available from: http://dx.doi.org/10.1016/j.envpol.2009.05.051
24. Rawat D, Nair D. Extended-spectrum ß-lactamases in Gram Negative Bacteria. 2010;(3).
25. Sharif MR, Soltani B, Moravveji A, Erami M, Soltani N. Prevalence and Risk Factors associated with Extended Spectrum Beta Lactamase Producing Escherichia coli and Klebsiella pneumoniae Isolates in Hospitalized Patients in Kashan (Iran). 2016;(March):2081–7.
26. Warren RE, Harvey G, Carr R, Ward D, Doroshenko A. Control of infections due to extended-spectrum b -lactamase-producing organisms in hospitals and the community. Clin Microbiol Infect [Internet]. 2008;14:124–33. Available from: http://dx.doi.org/10.1111/j.1469-0691.2007.01870.x
27. Chan M, Chiu S, Hsueh P, Wang N, Wang C. Risk Factors for Healthcare-Associated Extensively Drug-Resistant Acinetobacter baumannii Infections : A Case-Control Study. 2014;9(1).
28. Kramer A, Schwebke I, Kampf G. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. 2006;8:1–8.
29. Lee H, Koh YM, Kim J, Lee J, Lee Y, Seol S, et al. Capacity of multidrug-resistant clinical isolates of Acinetobacter baumannii to form biofilm and adhere to epithelial cell surfaces. Clin Microbiol Infect [Internet]. 2007;14(1):49–54. Available from: http://dx.doi.org/10.1111/j.1469-0691.2007.01842.x
30. Nseir S, Blazejewski C, Lubret R, Wallet F, Courcol R, Durocher A. Risk of acquiring multidrug-resistant Gram-negative bacilli from prior room occupants in the intensive care unit. Clin Microbiol Infect [Internet]. 2010;17(8):1201–8. Available from: http://dx.doi.org/10.1111/j.1469-0691.2010.03420.x
31. Knobler, S. L., Lemon, S. M., Najafi M& BT. The Resistance Phenomenon in Microbes and Infectious Disease Vectors: Implications for Human Health and Strategies for Containment - Workshop Summary. Washington: National Academies Press (US). Knobler SL, Lemon SM, Najafi M, Burroughs T, editors. Washington (DC); 2003.